Complete Summary

GUIDELINE TITLE

Anticoagulation therapy supplement.

BIBLIOGRAPHIC SOURCE(S)

Institute for Clinical Systems Improvement (ICSI). Anticoagulation therapy supplement. Bloomington (MN): Institute for Clinical Systems Improvement (ICSI); 2006 Apr. 49 p. [91 references]

GUIDELINE STATUS

This is the current release of the guideline.

This guideline updates a previous version: Anticoagulation therapy supplement. Bloomington (MN): Institute for Clinical Systems Improvement (ICSI); 2005 Apr. 65 p.

COMPLETE SUMMARY CONTENT

SCOPE

DISEASE/CONDITION(S)

- Conditions that require anticoagulation therapy (e.g., thrombosis)
- Conditions that may result from anticoagulation therapy (e.g., bleeding)

GUIDELINE CATEGORY

Management
Prevention
Risk Assessment

CLINICAL SPECIALTY

Cardiology
Emergency Medicine
Family Practice
Hematology
Internal Medicine
Neurology

INTENDED USERS

Advanced Practice Nurses
Allied Health Personnel
Health Care Providers
Health Plans
Hospitals
Managed Care Organizations
Nurses
Pharmacists
Physician Assistants
Physicians

GUIDELINE OBJECTIVE(S)

- To provide a resource for the clinician in the use of anticoagulant drugs
- To help physicians make risk-benefit treatment decisions
- To serve as a tool to use for patients treated with anticoagulants
- To bring about consistency in recommendations that are common to the scope of related Institute for Clinical Systems Improvement (ICSI) cardiovascular guidelines: Atrial Fibrillation; Heart Failure in Adults; Diagnosis and Initial Treatment of Ischemic Stroke; Diagnosis and Treatment of Chest Pain and Acute Coronary Syndrome (ACS); Venous Thromboembolism, and Venous Thromboembolism Prophylaxis for Surgical/Trauma Patients.

TARGET POPULATION

Any patient receiving anticoagulation therapy

Note: Refer to related National Guideline Clearinghouse (NGC) summaries of the Institute for Clinical Systems Improvement (ICSI) cardiovascular guidelines for specific target populations: Atrial Fibrillation; Heart Failure in Adults; Diagnosis and Initial Treatment of Ischemic Stroke; Diagnosis and Treatment of Chest Pain and Acute Coronary Syndrome (ACS); Venous Thromboembolism, and Venous Thromboembolism Prophylaxis for Surgical/Trauma Patients.

INTERVENTIONS AND PRACTICES CONSIDERED

1. Anticoagulants
    - Warfarin
    - Unfractionated standard heparin (UFH)
    - Low-molecular-weight heparin (LMWH)

    - Synthetic pentasaccharide (fondaparinux)
    - Alternative agents in selected cases: such as direct thrombin inhibitors
2. Reversal of anticoagulation
    - Vitamin K
    - Fresh frozen plasma (FFP)
    - Protamine sulfate
3. Patient education
4. Monitoring of anticoagulation therapy by establishing target international normalized ratios (INRs) or by using activated partial thromboplastin times (aPTTs) or heparin assays or by performing periodic platelet counts
5. Bridging therapy (e.g., taking a patient off warfarin in the perioperative setting and "bridging" with heparin)

MAJOR OUTCOMES CONSIDERED

Safety and Efficacy of Anticoagulation

- Risk and incidence of adverse effects of anticoagulation, (e.g., major bleeding, skin necrosis, heparin induced thrombocytopenia)
- Therapeutic anticoagulation levels (e.g., international normalized ratio [INR])

METHODOLOGY

METHODS USED TO COLLECT/SELECT EVIDENCE

Searches of Electronic Databases

DESCRIPTION OF METHODS USED TO COLLECT/SELECT THE EVIDENCE

Not stated

NUMBER OF SOURCE DOCUMENTS

Not stated

METHODS USED TO ASSESS THE QUALITY AND STRENGTH OF THE EVIDENCE

Not stated

RATING SCHEME FOR THE STRENGTH OF THE EVIDENCE

Not applicable

METHODS USED TO ANALYZE THE EVIDENCE

Systematic Review

DESCRIPTION OF THE METHODS USED TO ANALYZE THE EVIDENCE

Not stated

METHODS USED TO FORMULATE THE RECOMMENDATIONS

Not stated

RATING SCHEME FOR THE STRENGTH OF THE RECOMMENDATIONS

Not applicable

COST ANALYSIS

A formal cost analysis was not performed and published cost analyses were not reviewed.

METHOD OF GUIDELINE VALIDATION

Clinical Validation-Pilot Testing
Internal Peer Review

DESCRIPTION OF METHOD OF GUIDELINE VALIDATION

Institute Partners: System-Wide Review

The guideline annotation, discussion, and measurement specification documents undergo thorough review. Written comments are solicited from clinical, measurement, and management experts from within the member groups during an eight-week review period.

Each of the Institute's participating member groups determines its own process for distributing the guideline and obtaining feedback. Clinicians are asked to suggest modifications based on their understanding of the clinical literature coupled with their clinical expertise.

Representatives from all departments involved in implementation and measurement review the guideline to determine its operational impact. Measurement specifications for selected measures are developed by the Institute for Clinical Systems Improvement (ICSI) in collaboration with participating member groups following implementation of the guideline. The specifications suggest approaches to operationalizing the measure.

Guideline Work Group

Following the completion of the review period, the guideline work group meets 1 to 2 times to review the input received. The original guideline is revised as necessary, and a written response is prepared to address each of the responses received from member groups. Two members of the Cardiovascular Steering Committee carefully review the input, the work group responses, and the revised draft of the guideline. They report to the entire committee their assessment of four questions: (1) Is there consensus among all ICSI member groups and hospitals on the content of the guideline document? (2) Has the drafting work

group answered all criticisms reasonably from the member groups? (3) Within the knowledge of the appointed reviewer, is the evidence cited in the document current and not out-of-date? (4) Is the document sufficiently similar to the prior edition that a more thorough review (critical review) is not needed by the member group? The committee then either approves the guideline for release as submitted or negotiates changes with the work group representative present at the meeting.

Pilot Test

Member groups may introduce the guideline at pilot sites, providing training to the clinical staff and incorporating it into the organization's scheduling, computer, and other practice systems. Evaluation and assessment occur throughout the pilot test phase, which usually lasts for three to six months. At the end of the pilot test phase, ICSI staff and the leader of the work group conduct an interview with the member groups participating in the pilot test phase to review their experience and gather comments, suggestions, and implementation tools.

The guideline work group meets to review the pilot sites' experiences and makes the necessary revisions to the guideline, and the Cardiovascular Steering Committee reviews the revised guideline and approves it for release.

RECOMMENDATIONS

MAJOR RECOMMENDATIONS

Note from the National Guideline Clearinghouse (NGC) and the Institute for Clinical Systems Improvement (ICSI): In addition to updating their clinical guidance, ICSI has developed a new format for all guidelines. Key additions and changes include: combination of the annotation and discussion section; the addition of "Key Points" at the beginning of most annotations; the inclusion of references supporting the recommendations; and a complete list of references in the Supporting Evidence section of the guideline. For a description of what has changed since the previous version of this guidance, refer to "Summary of Changes -- April - 2006."

These recommendations supplement the recommendations on anticoagulation therapy provided in the National Guideline Clearinghouse (NGC) summaries of the Institute for Clinical Systems Improvement (ICSI) guidelines: Atrial Fibrillation; Heart Failure in Adults; Diagnosis and Initial Treatment of Ischemic Stroke; Diagnosis and Treatment of Chest Pain and Acute Coronary Syndrome (ACS); Venous Thromboembolism, and Venous Thromboembolism Prophylaxis for Surgical/Trauma Patients.

Class of evidence (A-D, M, R, X) ratings are defined at the end of the "Major Recommendations" field.

Clinical Highlights and Recommendations

1. There are no circumstances under which patients absolutely should or should not receive anticoagulation therapy. Clinicians must consider the risks and benefits of anticoagulation therapy for a patient based upon the individual's

risk for thrombosis if not treated weighed against the risk of bleeding if treated. (Introduction, Annotations #2, 3, 4, 11, 12, 13, 14)
2. In the initial phase of treatment for patients with active thrombosis (such as acute deep vein thrombosis [DVT]) or high risk of thrombosis, immediate-acting anticoagulant agents (unfractionated heparin [UFH]/low-molecular-weight heparin [LMWH]/fondaparinux) should be used concomitantly with warfarin. (Annotation #7)
3. Loading doses and rapid induction of warfarin (Coumadin®) should be avoided. (Annotation #7)
4. Many prescription medications or over-the-counter remedies, including dietary supplements and herbs, may alter the effectiveness of anticoagulants (detected by the international normalized ratio [INR]) and/or reduce the effectiveness of platelets (not detected by the INR). (Annotations #7; see also Annotations Appendices C, D, E in the original guideline document)
5. Vitamin K may be used to reverse supratherapeutic anticoagulation with warfarin. The dose of vitamin K depends upon the degree of INR elevation and/or signs and symptoms of bleeding (refer to Table 2 in the original guideline document). Vitamin K can lead to warfarin resistance and subsequently to an increased risk of thromboembolism. (Annotation #8)
6. Regardless of the anticoagulant used, it is important that patients know they must always inform their physician and other health care providers that they are on anticoagulation therapy, especially if they are potentially undergoing an invasive procedure. (Annotations #6, 21; see also Appendix E in the original guideline document)
7. Patients should be encouraged and empowered to play an active role in the self-management of their treatment. Self-management is best initiated and sustained through active involvement of patients and family members with their multidisciplinary health care team. This educational partnership should be encouraged to decrease potential risks and improve understanding of the importance of patient adherence to their treatment regimen. (Annotation #6, 21; see also Appendix E in the original guideline document)
8. Patients with mechanical heart valves and who are pregnant have complex anticoagulation needs and should be managed by an anticoagulation expert. (Annotations #4,13, 30)

Warfarin

1. Introduction

Warfarin is used in the chronic management of patients with several types of thrombotic diseases. It produces its anticoagulant effect by inhibiting the vitamin K dependent production of clotting factors II, VII, IX, X, and proteins C and S. Warfarin is not fully effective in the initial several days of therapy because of a delayed reduction in some of the clotting factors that it inhibits. In the initial phase of treatment for patients with active thrombosis (such as acute deep vein thrombosis [DVT]) or high risk of thrombosis, immediate acting anticoagulant agents (unfractionated heparin [UFH], low-molecular-weight heparin [LMWH], fondaparinux, direct thrombin inhibitors [DTIs]) should be used concomitantly with warfarin.

Evidence supporting this recommendation is of class: R

When determining the efficacy and tolerability of warfarin in patients with nonvalvular atrial fibrillation, the clinical trials excluded patients using the following criteria:

Table 1: Exclusion Criteria Used in Trials Evaluating the Efficacy and Tolerability of Anticoagulation in Patients with Nonvalvular Atrial Fibrillation

Active bleeding
Active peptic ulcer disease
Known coagulation defects
Thrombocytopenia (platelet less than 50,000/mm^3) or platelet dysfunction
Recent hemorrhagic stroke
Noncompliant or unreliable patients
Patient is psychologically or socially unsuitable
Dementia or severe cognitive impairment
History of falls (3 within the previous year or recurrent, injurious falls)
Excessive alcohol intake
Uncontrolled hypertension (greater than 180/100 mm Hg)
Daily use of nonsteroidal anti-inflammatory drugs (NSAIDs)
Planned invasive procedure or major surgery

Evidence supporting this recommendation is of class: R

The clinician will need to balance the potential increased risk in bleeding against the potential decreased risk of thromboembolism when evaluating warfarin therapy.

2. Contraindications

Key Points:

- All contraindications are relative to a patient's risk for thrombosis weighed against their risk for bleeding while on anticoagulation therapy.

Warfarin Allergy or Intolerance

Acute rash, hepatitis, diarrhea, or nausea may indicate an allergy or intolerance to warfarin.

Hemorrhage

Anticoagulation with warfarin is contraindicated in patients with active hemorrhage with possible exceptions in certain circumstances such as disseminated intravascular coagulation as a result of malignancy. The decision to initiate anticoagulation should be individualized for patients with a history of recent hemorrhage. Again, this is dependent on circumstances including the type of hemorrhage and the indication for anticoagulation. Withholding anticoagulation for 4 to 6 weeks may be prudent for non-central nervous

system bleeds. This duration may be longer for central nervous system (CNS) bleeds and needs to be assessed on a case-by case basis.

See Appendix A, "Risk Factor for Bleeding During Warfarin Therapy" and Annotation #3, "Adverse Effects" in the original guideline document for additional information about predicting the risk of bleeding for individual patients.

Pregnancy

See Annotation #4, "Pregnancy - Contraindicated."

3. Adverse Effects

Key Points:

- The most common adverse effect of warfarin is bleeding. Risk factors for bleeding include patient-related and treatment-related factors.

Bleeding

Patients treated with usual doses of warfarin have a 2-4% risk per year of bleeding episodes requiring transfusion, and a 0.2% risk per year of fatal hemorrhage. Risk factors for bleeding include patient-related factors and treatment-related factors.

Patient-related factors include age, previous episodes of bleeding, anemia (hematocrit [HCT] less than 30%), hypertension, heart disease, cerebrovascular disease, renal disease, history of gastrointestinal (GI) hemorrhage, active peptic ulcer disease or liver disease, recent or imminent surgery, trauma, excessive alcohol intake, unreliability, frequent or significant falls, regular use of NSAIDs, and use of other medications or natural remedies.

Treatment-related factors include duration, intensity and variability of warfarin treatment, concomitant use of aspirin, and support patients receive from their providers and home environments. Please refer to Appendix A, "Risk Factors for Bleeding During Warfarin Therapy" in the original guideline document for additional information on bleeding risk in anticoagulation therapy.

Risk factors for bleeding should not be considered absolute contraindications to anticoagulant therapy. Some risk factors for bleeding (such as age) are also risk factors for thromboembolism. The potential increased risk of bleeding must be balanced against the potential decreased risk of thromboembolism.

Evidence supporting this recommendation is of classes: A, B, C, D, R

Skin Necrosis

Skin necrosis is a rare but serious complication of warfarin therapy that typically occurs on the third to eighth day of therapy. Warfarin should be discontinued in patients with evidence of skin necrosis.

When warfarin-induced skin necrosis is suspected, patients should be placed on heparin therapy unless there is evidence of heparin induced thrombocytopenia (HIT).

Purple Toe Syndrome

Purple toe syndrome and other manifestations of peripheral emboli may rarely complicate warfarin therapy, usually 3 to 10 weeks after initiation of therapy. Causes of purple toe syndrome other than warfarin should be considered when making a treatment decision. These include vasculitis, acute myocardial infarction (MI) with embolism, and diabetes mellitus.

Less Serious Adverse Effects

Adverse effects that are less serious include alopecia, osteoporosis, gastrointestinal discomfort, and rash. Management of these adverse effects should be managed on an individual basis.

Evidence supporting this recommendation is of classes: B, D, R

4. Pregnancy - Contraindicated

Warfarin is contraindicated during pregnancy because it crosses the placenta causing teratogenicity and fetal bleeding. Unfractionated and low molecular weight heparins do not cross the placenta and do not cause teratogenicity or fetal bleeding. Therefore, unfractionated heparin (UFH) or a low-molecular-weight heparin (LMWH) should be used in place of warfarin. A recent study has shown that two pregnant patients with mechanical heart valves had thrombotic complications when treated with LMWH. Patients with mechanical heart valves and who are pregnant are at high risk and should be managed by an anticoagulation expert.

5. Breast Feeding

The amount of warfarin in breast milk is too small to affect the baby. As a result, breastfeeding is safe for mothers taking warfarin and for their infants.

6. Monitoring

Test

The INR is the preferred test for monitoring warfarin therapy. There are several recognized limitations of the test, including instrumentation effect on the ISI and erroneous reporting of the ISI by the thromboplastin manufacturer.

$$\text{The INR} = (\text{Patient PT}/\text{Mean Normal PT})^{\text{ISI}}$$

Where "PT" is prothrombin time, and the "ISI" is the International Sensitivity Index assigned to the thromboplastin used in the test.

During initiation of warfarin, the dose-response relationship is best interpreted when at least 16 hours elapse between dose and lab draw.

INR determinations should be obtained monthly in most stable patients, and no more than 6 weeks should elapse between determinations.

Heparin and lupus anticoagulants may spuriously prolong INR results obtained by some instrument-reagent combinations.

- Patients with a lupus anticoagulant may require a higher target therapeutic range than patients lacking a lupus anticoagulant.
- Lupus anticoagulants can cause a prolongation of the PT and INR resulting in an overestimation of a patient's anticoagulation. This effect is dependent on the thromboplastin that is used for the test.
- Clinically significant alterations of the INR due to a lupus anticoagulant can occur during warfarin therapy despite a normal baseline PT/INR.
- Measurement of chromogenic Factor X levels may be helpful in the monitoring of warfarin therapy in patients with lupus anticoagulant.

Blood Samples

Patient samples should be collected in 109 mmol/L (3.2%) sodium citrate when INR testing is performed on anticoagulated plasma.

- The volume of sodium citrate in blood tubes used for collection of plasma INR testing should be adjusted when the patient's hematocrit is greater than 55%. Specimens with a high hematocrit will cause spuriously high INR values unless the citrate volume is adjusted.
- Anticoagulated whole blood may be stored spun or unspun at room temperature for up to 24 hours prior to testing.

Evidence supporting this recommendation is of classes: B, D, R

Refer to the original guideline document for information on instruments including point of care instruments and reagents.

7. Dosing

Key Points:

- Loading doses of warfarin should be avoided.
- Patients receiving warfarin for the first time should begin at an average dose of 5 mg daily with a recheck of INR in 2-3 doses.
- Steady-state INR values will not be realized for up to 3 weeks following a dose adjustment.

General Principles of Warfarin Dosing

Loading doses and rapid induction of warfarin should be avoided. Warfarin (irrespective of INR) is not fully effective in the first several days of therapy because of a delayed decrease in several circulating clotting factors. Loading doses can increase a patient's risk of supratherapeutic INR and make it more difficult to determine a steady-state dose.

Patients at high risk of thrombosis, such as those with an active thrombotic process (e.g., venous thromboembolism [VTE]) or an underlying malignancy, should be treated with concomitant immediate-acting anticoagulant (UFH, LMWH, fondaparinux, DTIs) and warfarin therapy. Patients at lower thrombotic risk (e.g., atrial fibrillation without recurrent thromboembolism) can be initiated on warfarin alone.

A single target INR value should be used as a goal endpoint. This will decrease the odds of a patient being above or below desirable range of INR. The target INR for most conditions is 2.5 with an acceptable range of 2.0 to 3.0. Other thrombotic conditions (e.g., mitral mechanical valves) have recommended targets of 3.0 (range 2.5 to 3.5). A table of recommended therapeutic ranges for oral anticoagulant therapy is attached in Appendix B of the original guideline document. Also, individual disease management guidelines such as Atrial Fibrillation and Venous Thromboembolism give specific INR recommendations.

The risk of bleeding for patients on warfarin increases substantially at INR values greater than 4.0. This risk is magnified if one or more risk factors are present. Consider hemorrhagic risk in all dosing decisions. Please refer to Appendix A, "Risk Factors for Bleeding During Warfarin Therapy," of the original guideline document for more information on risk factors for bleeding during warfarin therapy.

There is a significant increase in thromboembolism as INR values decrease below INR 1.7. Clinical risk and past medical history should be considered in all dosing decisions. Higher risk may require more aggressive dosing.

In most cases, holding warfarin for 4 days prior to surgery results in an INR value of 1.2 or less. Expect advanced age and drug interactions to result in a slower decline. Patients with high risk of thromboembolism may need coverage with heparin for a portion of this time. For more information, see Annotation #30, "Perioperative Anticoagulation (including Bridging)."

Some equivalency studies have shown that substitution of generic warfarin for brand name Coumadin® may provide equivalent anticoagulation response if the manufacturer of the generic warfarin has followed the standards set for the name brand. Care must be taken to remain with either the brand name product or the same generic product. Do not switch from brand to generic or between generics.

Prescription and over-the-counter medications can adversely affect the INR response to warfarin. Dietary supplements including herbal or natural remedies can change the INR response to warfarin and/or increase a patient's risk of bleeding. In these instances, additional monitoring may be needed. See Appendices C, "Drug Interactions with Warfarin" and D, "Endogenous

Interactions with Warfarin" in the original guideline document for more information on drug interactions with warfarin.

Mechanism of drug-drug interactions occur commonly by the cytochrome P450 enzyme metabolizing system. Metabolism of the object or substrate medication may either be induced or inhibited by the interacting drug. Induction will result in a diminished pharmacodynamic response, while inhibition will result in an increased pharmacodynamic response.

Foods that contain moderate amounts of vitamin K may decrease the INR response to warfarin. See Annotation #9, "Key Patient Education Components" for a guide to educating patients regarding warfarin therapy in the original guideline document.

Direct thrombin inhibitors (hirudin, argatroban, bivalirudin) and heparins can affect the INR. See Annotation #29, "Direct Thrombin Inhibitors" in the original guideline document for more information on direct thrombin inhibitors.

Evidence supporting this recommendation is of classes: A, B, D, R

Initiation of Warfarin

Average Daily Dosing Technique (for patients not on heparin)

Average daily dosing technique is useful for patients off UFH and LMWH.

A baseline INR value may be drawn to rule out underlying coagulopathy.

Patients previously taking warfarin can be initiated at the previous dose.

Patients receiving warfarin for the first time should begin at an average dose of 5 mg daily with a recheck of INR in 2 to 3 doses. Lower initiation doses should be considered for patients with any of the following factors: age greater than 75 years, multiple comorbid conditions, poor nutrition (low albumin), elevated INR when off warfarin, elevated liver function tests, or changing thyroid status. For patients who weigh more than 80 kg, a higher estimated average initial dose of 7.5 mg may be given. Higher initial dosing nomograms have not shown consistent benefit. Loading doses can increase a patient's risk of supratherapeutic INR and make it more difficult to determine a steady-state dose.

If the INR is 2.0 or greater after the first 3 doses, consider decreasing the dose by one-half. Always search for causes of rapid rise in INR such as poor nutritional status, infection, or systemic disease process. See Appendix D in the original guideline document for more information on endogenous interactions with warfarin.

Subsequent INR values are determined at 2 to 3 times weekly for 1 to 2 weeks, then less often depending on the stability of the INR result.

Steady state anticoagulation occurs between 6 to 12 days. Expect obese patients and patients of advanced age to take longer to reach steady state.

Evidence supporting this recommendation is of class: A

Flexible Daily Dosing Technique (for patients on heparin)

The flexible daily dosing technique is useful for patients on concomitant UFH or a LMWH.

A baseline INR value may be drawn to rule out underlying coagulopathy.

Patients are given daily doses of warfarin, adjusted according to the daily INR, until a weekly dose can be determined.

The dose-response relationship is best interpreted when there are at least 16 hours between dose and laboratory draw.

Evidence supporting this recommendation is of class: D

Maintenance Dosing of Warfarin

An assessment of clinical variables known to affect the INR (including a change of patients adherence, change of other medications (e.g., amiodarone), change of food or alcohol consumption, change of activity level should be made with each dose adjustment. Always search for the cause of out-of-range values and address them before adjusting the dose.

Expect a 15% dose adjustment to result in an approximately 1.0 INR change. Likewise, a 10% dose adjustment will result in an approximate 0.7 to 0.8 INR change.

Steady-state INR values will not be realized for up to 3 weeks following a dose adjustment.

Patients with INR values $\pm$ 0.5 INR out-of-range should be considered for more frequent monitoring and should have a repeat INR within seven days.

If two consecutive weekly INR values are within range and there has not been a change in clinical variables known to effect the INR, the interval between draws may be gradually increased to monthly, and not more than 6 weeks.

Options for Dosing and Management

Anticoagulation clinics have been shown to significantly reduce patients risks of adverse events.

Though traditionally, warfarin has been monitored at a central laboratory and managed by the patient's physician, new monitoring and management options have emerged.

Anticoagulation clinics staffed by pharmacists/registered nurses (RNs) have been shown to significantly reduce patients' risks of adverse events.

Computer-assisted dosing has been slow to develop, but may someday improve the quality of anticoagulation adjustments and offer superior management for difficult or high-risk patients.

Selected point-of-care instruments have received U.S. Food and Drug Administration (FDA) approval for patient self-testing.

While some patients may prefer self-management, clinical experience, reimbursement, and research are insufficient to support widespread implementation of patient self-management. Further research is needed to better identify appropriate candidates for self-management, and to delineate the key components of education and support.

Evidence supporting this recommendation is of classes: B, C, D, R

8. Correction of Supratherapeutic Anticoagulation Caused by Warfarin

Supratherapeutic anticoagulation may occur with patients taking warfarin. Vitamin K may be used to reverse the effects of warfarin; however, vitamin K can lead to warfarin resistance and, subsequently, to an increased risk of thromboembolism.

Important Considerations for Vitamin K Dosing

In an outpatient clinic setting, oral vitamin K is the preferred route of administration.

In a hospital setting, when patients are ill or taking nothing per mouth (NPO), intravenous vitamin K may be the preferred route of administration. To avoid anaphylactic reactions, vitamin K should be given over 30 minutes in a mixture of dextrose 5% in water (D5W) 50 mL under monitored conditions. It is not necessary to premedicate with corticosteroids or antihistamines.

Administration of vitamin K by subcutaneous or intramuscular injection are not recommended due to unpredictable absorption which can lead to erratic correction of the INR and resistance to warfarin.

Refer to Table 2 in the original guideline document for details on correction of supratherapeutic warfarin anticoagulation caused by warfarin.

9. Key Patient Education Components

Mechanism of action of warfarin: it depletes certain coagulation factor proteins in the blood.

Time of day to take warfarin: it should be taken at approximately the same time and each day. Due to the short half-life of factor VII and its influence on

the INR, this is especially important if the patient will have an INR drawn the next morning.

Explanation of INR, target range, and regular testing

Signs and symptoms of bleeding and that the provider should be contacted immediately if bleeding signs are present.

Need to notify provider if illness, injury, or change in physical status occurs.

Need to inform all their health care providers of anticoagulation therapy, especially if potentially undergoing an invasive procedure, surgery or dental work.

Drug interactions:

- What to do if a new medication is initiated or a medication is discontinued, especially if the interaction with warfarin is unknown: check INR within 3 to 4 days.
- Drugs that affect the absorption of warfarin
- Drugs that increase or decrease the effect of warfarin
- Common over-the-counter medication interactions, including aspirin, non-steroidal anti-inflammatory drugs (NSAID), acetaminophen, natural or herbal remedies, laxatives, antacids, and multivitamin preparations containing vitamin K

Role of vitamin K and the importance of consistency of vitamin K rich foods in the diet rather than avoidance of vitamin K rich foods.

Importance of minimizing trauma risk associated with activities at high risk for injury.

Effect of exercise: increased activity results in decreased effect of the drug

Effect of personal habits: alcohol, chewing tobacco, etc.

Effect of certain conditions: congestive heart failure, thyroid disease, gastroenteritis, and diarrhea

Importance of self-monitoring: maintain a log of INRs, dose of warfarin, etc.

Medic Alert bracelet/necklace and warfarin ID card.

See Appendix E in the original guideline for a guide to patient education regarding warfarin therapy.

Heparin (Unfractionated and Low-Molecular-Weight Heparin) and Synthetic Pentasaccharide (Fondaparinux)

10. Introduction

Heparin's (UFH, LMWH) anticoagulant effect is due to the presence of a pentasaccharide sequence which potentiates the action of antithrombin III leading to inactivation of several clotting factors--primarily factors Xa and IIa. Heparins have relatively rapid onset of action compared to warfarin and are often the first drug used in acute thrombotic situations.

UFH is derived from porcine or bovine sources. It has variable absorption, metabolism, and pharmacokinetics and effects on anticoagulation. Monitoring is required in most patients treated with this drug.

LMWH are depolymerized byproducts of UFH. Pharmacological advantages of LMWH relate to superior absorption and consistent dose effect response.

Fondaparinux is a synthetic compound composed of the essential pentasaccharide sequence.

11. Contraindications

Active major bleeding including intracerebral hemorrhage within past two weeks, subarachnoid hemorrhage until definitively treated.

Thrombolytics given within past 24 hours for acute stroke.

Hypersensitivity to heparin or pork products.

Heparin-induced thrombocytopenia (HIT).

Renal failure (LMWH and fondaparinux).

Fondaparinux has a long elimination half-life and there is no antidote for reversal; therefore, patients who may require rapid reversal are not candidates for this therapy.

12. Precautions

Active or history of recent gastrointestinal ulceration and hemorrhage.

Bacterial endocarditis.

Bleeding diathesis.

Concomitant therapy with agents that inhibit platelets.

Congenital or acquired bleeding disorders.

Hemorrhagic stroke.

Status post brain, spinal, or ophthalmologic surgery.

Uncontrolled arterial hypertension.

Diabetic retinopathy.

13. Adverse Effects

Key Points:

- Heparin-induced thrombocytopenia (HIT) should be suspected in patients who develop a skin lesion reaction at the injection site, have a systemic reaction to a bolus administration of heparin, or develop a greater then 50% decrease in platelet count from baseline labs while on heparin.
- All heparin should be stopped in patients suspected on having HIT until antibody test results are available.
- If the patient is on concomitant warfarin and HIT is suspected, the warfarin should be stopped, the warfarin effects corrected, and patient started on DTI therapy.

Bleeding

Risk of bleeding increases with treatment -related factors such as dose, duration, and use of thrombolytics and/or antiplatelet agents, and patient-related factors including age over 70 years, recent trauma or surgery, coagulopathy, peptic ulcer, neoplasm, or renal failure.

Evidence supporting this recommendation is of classes: A, R

Heparin-Induced Thrombocytopenia (HIT)

HIT is an immune-mediated reaction to heparins. It occurs in 2 to 3% of patients treated with UFH and less than 1% of patients treated with LMWH. This syndrome can be associated with paradoxical increased risk for venous and arterial thrombosis. Patients who develop HIT without associated thrombosis will have a significant risk for thrombosis in the subsequent 100 days. Patients with a history of HIT should not be treated with UFH or LMWH.

HIT should be suspected in patients who develop a skin lesion reaction at the injection site, have a systemic reaction to a bolus administration of heparin, or develop a greater than 50% decrease in platelet count from baseline labs while on heparin. These patients should have their heparin stopped while antibody testing for HIT is performed. Patients with a high clinical probability of having HIT should be treated with an appropriate alternative anticoagulant before antibody test results are available. Direct thrombin inhibitors (DTIs) are the alternative anticoagulant of choice for patients with HIT. Three brands are FDA approved: lepirudin (Refludan®), argatroban, and most recently bivalirudin (Angiomax®).

Although in vitro data have not demonstrated cross reactivity of fondaparinux with HIT antibodies, additional studies are needed before its use can be considered.

If a patient is receiving warfarin when there is a high clinical probability of HIT, the warfarin should be stopped. The warfarin effect should be reversed with vitamin K and DTI therapy should be initiated. Low maintenance doses of warfarin can be restarted during DTI therapy after the platelet count has significantly improved and there is clinical improvement in the patient's thrombosis. There should be at least a 5-day overlap of the DTIs and warfarin. The DTI therapy should be continued until the platelet count stabilizes.

See Annotation #29, "Direct Thrombin Inhibitors" in the original guideline document for more information on direct thrombin inhibitors.

Evidence supporting this recommendation is of class: R

14. Pregnancy

Adverse Effects in Pregnancy

UFH and LMWH do not cross the placenta and therefore do not cause teratogenicity or fetal bleeding, though bleeding at the uteroplacental junction is possible.

Patients with mechanical heart valves and who are pregnant are at high risk and should be managed by an anticoagulation expert. A study has shown that two pregnant patients with mechanical heart valves had thrombotic complications when treated with LMWH. Because of this, the Food and Drug Administration (FDA) and the manufacturer have warned that enoxaparin is not presently indicated for use in prophylaxis for heart valve patients who are pregnant. However, the available data sets, clinical trials, reviews, and registry data suggest that, compared with UFH, LMWHs may be safe and effective agents in pregnant women with mechanical heart valves.

The American College of Chest Physicians (ACCP) recommends that women requiring long-term anticoagulation with warfarin who are attempting pregnancy be monitored with frequent pregnancy tests. They recommend substituting UFH or a LMWH for warfarin when pregnancy is achieved. LMWHs cause less HIT and bone loss during pregnancy than UFH.

The pharmacokinetics of LMWH in pregnancy is significantly altered. Consideration should be given to monitoring the antifactor Xa activity at 12 to 15 weeks and 30 to 33 weeks.

When possible, patients using UFH or a LMWH should have a planned delivery. UFH should be discontinued 6 hours prior to a planned delivery. LMWH should be discontinued 24 hours prior to a planned delivery.

There is limited data on use of fondaparinux in pregnancy.

Evidence supporting this recommendation is of class: R

15. Breast Feeding

Heparin is not secreted in breast milk and can be given safely to nursing mothers.

It is unknown if fondaparinux is excreted in human breast milk. Animal studies have been positive for the secretion of fondaparinux in breast milk.

Unfractionated Heparin

16. Monitoring

UFH treatment of thrombosis can be monitored using an activated partial thromboplastin time (aPTT) or heparin assay. The recommended test for monitoring UFH, including the therapeutic range for the test, should be provided by the laboratory. Of note, aPTT results vary among institutions due to differences in laboratory instruments and reagents. The aPTT therapeutic range should correspond to a plasma heparin concentration of 0.3 to 0.7 units/mL by an antifactor Xa inhibition assay (0.2 to 0.4 units/mL by protamine titration assay).

Heparin assays are being increasingly used for monitoring UFHs in the treatment of venous thromboembolism. The suggested target therapeutic range is 0.35 to 0.7 units/mL by the antifactor Xa inhibition assay. Monitoring unfractionated heparin using a heparin assay may be indicated when the expected aPTT prolongation is not observed despite high doses of UFH (greater than 35, 000 U unfractionated heparin in 24 hours), when the pretreatment aPTT is prolonged or when a lupus anticoagulant has been previously documented in the patient.

Patients receiving UFH or a LMWH should be monitored for heparin-induced thrombocytopenia (HIT) with a platelet count beginning at baseline, then every other day. A platelet count of less than 50% of baseline may indicate the development of HIT.

Note: Patients who have not received heparin within the previous 3 months are unlikely to develop HIT within the first 3 days of treatment; however, patients who have received heparin within 3 months may develop HIT more rapidly. Unfortunately, patients are not always aware that they have received heparin (with surgery, central intravenous catheters, etc.) For the sake of safety and simplicity, the workgroup recommends a platelet count every other day for all patients receiving UFH or a LMWH. See Annotation #13, "Adverse Effects" for more information on adverse effects in the original guideline document.

Evidence supporting this recommendation is of classes: B, R

17. Dosing

Weight-based, institution specific nomograms are strongly recommended for patients on therapeutic intravenous UFH. Each institution must develop its own nomograms based upon their unique specific therapeutic ranges. See

Appendix F in the original guideline document for an example of a heparin nomogram.

A standard weight-based protocol for heparin administration should not be used for patients receiving parenteral platelet receptor glycoprotein IIb/IIIa antagonist (abciximab or ReoPro®), tirofiban (Aggrastat®), eptifibatide (Integrilin®), and/or thrombolytics (alteplase or Activase®). Treating physicians should refer to the specific agent's package insert or their institution protocols for the specific agent's heparin protocol.

Before administering UFH, the patient's height in centimeters and weight in kilograms and any adverse reactions to drugs or food, including a description of the reaction, should be noted.

Before administering UFH, draw hemoglobin/hematocrit, platelet count, activated partial thromboplastin time (aPTT) and prothrombin time (PT).

Initiation of UFH

An initial bolus dose of heparin is recommended followed by intravenous infusion, with the exception of acute stroke. The use of heparin in patients with acute stroke is controversial. See the NGC summary of the ICSI guideline Diagnosis and Initial Treatment of Ischemic Stroke. Note the time of initial heparin bolus.

After initial intravenous bolus of heparin, begin maintenance drip per institutional protocols.

Maintenance

Obtain an aPTT level or heparin assay six hours after the initiation of intravenous (IV) heparin drip. Adjust the IV drip according to institutional protocols.

Evidence supporting this recommendation is of classes: A, B

18. Correction of Supratherapeutic Anticoagulation Caused by UFH

Protamine sulfate administered by slow intravenous infusion over 10 minutes reverses the anticoagulation effects of unfractionated heparin.

$$\frac{\text{Bolus dose of UFH (units)}}{100} = \text{protamine dose}$$

$$\frac{\text{Hourly infusion rate of UFH (units)}}{40} = \text{protamine dose}$$

Anaphylaxis occurs in 1% of patients who have previously received protamine (such as NPH insulin). Other adverse effects include hypotension.

Evidence supporting this recommendation is of class: R

19. Key Patient Educational Components

Importance of understanding heparin assays, INRs, and target ranges

Know and watch for signs of bleeding

Low Molecular Weight Heparin (LMWH)

20. Precautions

Spinal or Epidural Anesthesia or Spinal Puncture

Regional anesthesia should be avoided in patients with a history of abnormal bleeding or if taking medications that affect hemostasis (e.g., aspirin, NSAIDs, platelet inhibitors, warfarin).

Bleeding or hematomas within the spinal column may result when a heparin product or fondaparinux is used concurrently with spinal or epidural anesthesia or spinal puncture. The risk for complication increases with placement or removal of catheters in the spinal canal and by traumatic or repeated epidural or spinal puncture. Use of other drugs affecting the blood clotting mechanism, such as NSAIDs, platelet inhibitors, or other anticoagulants, also increases the risk of complication.

- If a regional anesthetic is administered, a single-dose spinal anesthetic is preferable to continuous epidural anesthesia.
- If a continuous epidural anesthesia is administered, the decision to implement LMWH prophylaxis in the presence of an indwelling catheter must be made with extreme care. If LMWH prophylaxis is administered while the patient is receiving continuous epidural anesthesia, the patient must be monitored carefully for early signs of cord compression (e.g., progression of lower extremity numbness or weakness, or bowel or bladder dysfunction).
- If LMWH prophylaxis is administered while the patient is receiving continuous epidural anesthesia, removal of the catheter should be delayed at least 8 to 12 hours after the dose of LMWH. Regional anesthesia should be avoided if there is a hemorrhagic aspirate during insertion of the spinal needle.
- LMWH prophylaxis should be delayed 2 hours after placement of the spinal needle or removal of the catheter.
- Carefully monitor patients for possible spinal or epidural bleeding. Treat immediately if neurological impairment is detected.

Evidence supporting this recommendation is of classes: D, R

21. Monitoring

Patients receiving LMWH should be monitored for heparin induced thrombocytopenia (HIT) with a platelet count beginning at baseline, then every other day. See Annotation #13 for more information.

In most clinical situations, monitoring of LMWH is not required. Indications for monitoring of LMWH include renal insufficiency (calculated creatinine

clearance less than 30 mL/min), low body weight (less than 50 kg), obesity, and pregnancy.

The recommended test for monitoring LMWH is an antifactor Xa assay (heparin assay). An antifactor Xa assay standard curve must be constructed for each LMWH preparation used in the care system. Appropriate commercial controls can be used if available. Although the aPTT may be prolonged in patients on LMWH, it does not reliably reflect LMWH activity.

The suggested therapeutic range for twice-daily dosing is 0.6 to 1.0 IU/mL obtained 4 hours after subcutaneous injection. One suggested target range for once-daily dosing is 1.0 to 2.0 IU/mL obtained 4 hours after subcutaneous injection.

Evidence supporting this recommendation is of class: R

22. Dosing

LMWH should not be administered by intramuscular injection.

Therapeutic doses of a LMWH are different from prophylactic doses.

Doses of different LMWHs are not interchangeable.

The anticoagulant effect of LMWH can extend beyond 24 hours after administration.

The dose should be modified for patients with impaired renal function. It may be necessary to monitor the anti-Xa level in these patients. LMWHs are relatively contraindicated in patients with a creatinine clearance less than 30 or who are receiving dialysis. To calculate the estimated creatinine clearance, use the Cockcroft-Gault equation as follows:

In men:

Creatinine clearance =

$$\frac{(140 - \text{age}) \times \text{weight in kg}}{(72 \times \text{serum creatinine})}$$

In women:

Creatinine clearance =

$$\frac{(140 - \text{age}) \times \text{weight in kg} \times 0.85}{(72 \times \text{serum creatinine})}$$

The optimal dose of LMWH has not been established in patients with low body weight (less than 50 kg) (possibly higher than usual dose), obesity (possibly lower than usual dose), or pregnancy (changing dose due to changing

creatinine clearance). It may be necessary to monitor the anti-Xa level in these patients.

Evidence supporting this recommendation is of classes: A, D, R

Refer to Table 3 in the original guideline document for therapeutic dosing of LMWH and Table 4 for prophylactic dosing of LMWH.

23. Correction of Supratherapeutic Anticoagulation Caused by LMWH

No agent, including fresh frozen plasma (FFP) and vitamin K, is effective for complete reversal of supratherapeutic anticoagulation with LMWH. Reversal of LMWH with protamine sulfate may be incomplete, with neutralization of 60 to 75% at most. However, protamine should be considered in patients with severe life-threatening bleeding.

Protamine sulfate administered by slow IV infusion over 10 minutes reverses the anticoagulation effects of LMWH. Anaphylaxis occurs in 1% of patients who have previously received protamine (such as NPH insulin). Other adverse effects include hypotension.

If LMWH has been administered within the last 8 hours:

First dose: 1 mg protamine per 100 antifactor Xa units LMWH*

Second dose: 0.5 mg protamine per 100 antifactor Xa units LMWH*

Smaller doses are needed if the LMWH was administered more than 8 hours ago.

* 1 mg enoxaparin - approximately 100 antifactors Xa units

Evidence supporting this recommendation is of class: R

24. Key Patient education Components

Over-the-counter and prescription drugs which should not be taken while on LMWH.

Importance of understanding heparin assay, INRs and target ranges.

Know and watch for signs of bleeding

Proper technique for injecting LMWH.

Restrictions for other conditions including DVT, stroke, or coronary artery disease (CAD). Refer to related ICSI guidelines for more information.

Importance of adhering to prescribed regimen.

Tables of patient education resources, along with patient and provider-oriented websites, are attached in the Support for Implementation section of the original guideline document.

Synthetic Pentasaccharide (Fondaparinux)

25. Monitoring

The heparin assay (anti factor Xa) has been used to monitor effects of fondaparinux; however, in most clinical situations, monitoring may not be necessary. Indications for monitoring of fondaparinux include renal insufficiency (calculated creatinine clearance less than 30), low body weight (less than 50 kg) and obesity. There is limited data on use of fondaparinux in pregnancy.

A platelet count should be obtained prior to the initiation of fondaparinux. Theoretically, antibodies to fondaparinux do not interact with Platelet Factor 4, therefore fondaparinux should not cause HIT and it may even be used in HIT therapy someday. Additional platelet monitoring is not required. Fondaparinux is not recommended for patients with platelets less than 100,000 mm^3 due to the overall increased risk of bleeding.

Fondaparinux may cause transient elevations in serum aminotransferases. This effect is reversible and routine monitoring is not recommended.

Additional information on fondaparinux is included in the NGC summary of the ICSI guideline Venous Thromboembolism (VTE) Prophylaxis for Surgical/Trauma Patients.

Evidence supporting this recommendation is of classes: A, R

26. Dosing

Therapeutic doses are different than prophylactic dosing.

Fondaparinux is not recommended for patients with platelets less than 100,000 mm^3

The dose of fondaparinux should be modified in patients with renal impairment. Fondaparinux is relatively contraindicated in patients with a creatinine clearance less than 30 mL/min. Fondaparinux should not be used in patients who are receiving dialysis.

Fondaparinux is not recommended for patients weighing less than 50 kg.

The optimal dose of fondaparinux has not been established in patients with obesity (possibly lower than usual dose). It may be necessary to monitor the anti-Xa level in these patients.

There is limited data on use of fondaparinux in pregnancy.

See Table 6 in the original guideline document for information on FDA approval status, indications, and dosing of fondaparinux.

Evidence supporting this recommendation is of classes: A, M

27. Correction of Supratherapeutic Anticoagulation Caused by Fondaparinux

There is no antidote for excessive bleeding due to fondaparinux. Recombinate factor VIIa has shown promise as a possible antidote in studies utilizing healthy volunteers. Enzymes capable of degrading heparin have also been investigated as a future treatment for excessive bleeding due to fondaparinux.

28. Key Patient Education Components

Importance of understanding fondaparinux and target ranges.

Know and watch for signs of bleeding.

Proper technique for injecting fondaparinux.

Restrictions for other conditions including DVT, stroke, or coronary artery disease (CAD). Please refer to the related ICSI guidelines for more information.

Importance to adhering to prescribed regimen

29. Direct Thrombin Inhibitors

Direct Thrombin Inhibitors (DTIs) are a relatively new class of anticoagulant drugs. They exert their effect by directly attaching to both free and fibrin-bound thrombin. Potential advantages of these drugs over UFH are inhibition of fibrin (clot) bound thrombin, a more predictable anticoagulant response, and no effect on platelet factor 4. DTIs are presently approved for use in patients with active HIT and those with a previous history of HIT who require anticoagulation therapy. These drugs are also in varying stages of development for use in other thrombotic disease processes. Three available DTIs will be described for their use in HIT. It is strongly recommended that consultation with a hematologist or anticoagulation expert is done when using these new anticoagulant drugs because of both drug and disease complexities.

A. Lepirudin (recombinant hirudin) (Refludan®)

This is a potent specific inhibitor of thrombin that forms a slowly reversible complex with the enzyme by binding to both its active site and an exosite focus (bivalent effect). It is cleared predominantly by the kidneys with a half-life of 40 minutes post IV dose and 120 minutes post subcutaneous dose. It has almost irreversible binding to

thrombin and has been associated with an increased risk of major bleeds in one study.

The drug is dosed at 0.4 mg/kg bolus IV followed by 0.15 mg/kg/hour IV with adjustments to maintain aPTT at 1.5 to 2.5 times the median of the laboratory normal range. This range may not be appropriate if the patient's aPTT is elevated at baseline.

The ecarin clotting time and chromogenic hirudin assay have been shown to be superior tests for monitoring recombinant hirudin therapy. However, these tests are not yet widely available in clinical laboratories.

B. Bivalirudin (Angiomax®)

This is a semi-synthetic bivalent inhibitor of thrombin. However, unlike hirudin, bivalirudin produces only transient reversal of thrombin and a shorter half-life. It has minimal renal excretion.

Bivalirudin is dosed as a 1.0 mg/kg IV bolus followed by 2.5 mg/kg/hour for 4 hours followed by 0.2 mg/kg/hour infusion thereafter.

C. Argatroban (Acova®)

This is a small molecular weight reversible inhibitor of the active site of thrombin (univalent). This agent is excreted normally in patients with renal insufficiency, but the dose must be reduced in patients with hepatic failure.

Argatroban has a short half-life (less than 1 hour) and is dosed at 2 micrograms/kg/min with adjustments to maintain aPTT at 1.5 to 3.0 times normal (not to exceed 100s).

The major side effect of DTIs is bleeding. This appears to be more significant with the irreversible inhibitor Lepirudin and less so with the reversible inhibitors. There is no antidote for these medications should bleeding occur, which further supports the use of agents with a short half-life.

<u>Perioperative Anticoagulation (Including Bridging)</u>

30. Perioperative Anticoagulation (Including Bridging)

PERIOPERATIVE ANTICOAGULATION		Procedure Bleeding Risk	
		LOW	HIGH
Patient Thromboembolic Risk	LOW	Continue Warfarin	Hold Warfarin 4 Days Prior To The Procedure (see Table #5)
	HIGH	Continue Warfarin	Bridging

31. Risk of Thrombotic Complications in the Absence of Anticoagulation Therapy

Condition	% Thrombotic Risk (Annualized)
Atrial Fibrillation (lone)	1
Atrial Fibrillation (average risk)	5
Atrial Fibrillation (average risk)	5
Atrial Fibrillation (high risk)	12
Aortic Valve Prosthesis (dual-leaflet -- St. Jude)	10-12
Aortic Valve Prosthesis (single-leaflet -- Bjork-Shiley)	23
Mitral Valve Prosthesis (dual-leaflet -- St. Jude)	22
Multiple Prosthesis (St. Jude)	91

32. Low Bleeding Risk Procedures
33. For dental procedures, a review of the literature has shown that in most cases no change in warfarin is needed. It may be reasonable to allow the patient to "drift" to the lowest effective INR prior to a dental procedure. Local bleeding may be controlled with a variety of techniques including pressure, biting on tea bags, gelatin sponges and topical thrombin. Other means of local hemostasis control include tranexamic acid mouthwash or epsilon aminocaproic acid packing. Other examples of procedures with low bleeding risk include skin biopsies and cataract surgery. Patients who have procedures that are of low bleeding risk can be continued on warfarin anticoagulation without interruption.
34. Low Thromboembolic Risk Patients
35. Patients with low thromboembolic risk, such as patients with atrial fibrillation without prior cerebrovascular accident (CVA) or other thromboembolic event, may stop warfarin 4 doses prior to the procedure and resume warfarin the evening of surgery. Low thromboembolic risk patients undergoing procedures that require perioperative UFH or LMWH for VTE prophylaxis should receive the recommended prophylaxis in addition to resumption of warfarin.
36. Patients with Mechanical Heart Valves who are Pregnant or are Attempting Pregnancy -- Management by an Anticoagulation Expert
37. Patients with mechanical heart valves and who are pregnant are at high risk and should be managed by an anticoagulation expert. A study has shown that two pregnant patients with mechanical heart valves had thrombotic complications when treated with LMWH. Because of this, the FDA and manufacturer have warned that enoxaparin is not presently indicated for use in prophylaxis for heart valve patients who are pregnant.
38. High Bleeding Risk Procedures for High Thromboembolic Risk Patients -- Bridging
39. Table 5: Recommended Bridging Schedule
40. Please be aware that this schedule is not FDA-approved and there are no randomized controlled trials that have studied the efficacy of this schedule. An individual's history of thromboembolism will assist with the decision-making. In general, plan to skip 4 doses prior to the invasive procedure.

Days Before Procedure	Warfarin	INR	LMWH* or Therapeutic UFH
5 days prior to	Last dose	Check if not	4-5 days before

Days Before Procedure	Warfarin	INR	LMWH* or Therapeutic UFH
procedure		done within 2 weeks prior	procedure, start after first missed warfarin dose
4 days prior to procedure	None	None	4-5 days before procedure, start after first missed warfarin dose
3 days prior to procedure	None	None	AM and PM dose
2 days prior to procedure	None	None	AM and PM dose
1 day prior to procedure	None	Check INR; 1-2.5 mg by mouth Vitamin K as needed if INR greater than 1.5	AM dose only -- at least 18 hours between dose and procedure
Procedure	Resume at regular dose that evening	None	Start at least 12 hours post procedure -- see Annotation #19 of guideline
1 day after procedure	Regular dose	As indicated -- may be skipped	Restart if hemostasis achieved
2 days after procedure	Regular dose	As indicated	Restart if hemostasis achieved
3 days after procedure	Regular dose	As indicated	Continue until INR greater than minimum acceptable x 2 day
4 days after procedure	Regular dose	Daily until INR greater than 2.0, then as indicated	Discontinue

41. *If enoxaparin (Lovenox®) is used as the LMWH, dosing is every 12 hours (a.m. and p.m.). Once a day dosing is used if the LMWH is tinzaparin (Innohep®) or dalteparin (Fragmin®).
42. Perioperative Management of Antiplatelet Agents
43. Patients receiving anti-platelet agents should have these agents stopped 2 to 10 days prior to a procedure:
    - Plavix 7 days prior to surgery
    - Acetylsalicylic acid (ASA) 7-10 days prior to surgery
    - Ibuprofen 2 days prior to surgery
    - Pletal 5 days prior to surgery

    Evidence supporting this recommendation is of classes: D, R

31. Key patient Education Components

    If a patient is to receive bridging therapy, the patient or a caregiver must show proficiency in the injection technique and proficiency with adhering to the perioperative schedule.

Definitions:

Classes of Research Reports:

A. Primary Reports of New Data Collection:

Class A:

- Randomized, controlled trial

Class B:

- Cohort study

Class C:

- Non-randomized trial with concurrent or historical controls
- Case-control study
- Study of sensitivity and specificity of a diagnostic test
- Population-based descriptive study

Class D:

- Cross-sectional study
- Case series
- Case report

B. Reports that Synthesize or Reflect upon Collections of Primary Reports

Class M:

- Meta-analysis
- Systematic review
- Decision analysis
- Cost-effectiveness analysis

Class R:

- Consensus statement
- Consensus report
- Narrative review

Class X:

- Medical opinion

CLINICAL ALGORITHM(S)

None provided

EVIDENCE SUPPORTING THE RECOMMENDATIONS

TYPE OF EVIDENCE SUPPORTING THE RECOMMENDATIONS

The type of supporting evidence is classified for selected recommendations (see "Major Recommendations").

BENEFITS/HARMS OF IMPLEMENTING THE GUIDELINE RECOMMENDATIONS

POTENTIAL BENEFITS

- Guideline implementation may help the clinician make risk-benefit treatment decisions regarding anticoagulation therapy and appropriately manage patients on anticoagulation therapy to maximize safety and efficacy.
- There are no circumstances under which patients absolutely should or should not receive anticoagulation therapy. Clinicians must consider the risks and benefits of anticoagulation therapy for a patient based upon the individual's risk for thrombosis if not treated weighed against their risk of bleeding if treated.

POTENTIAL HARMS

- The major potential side effect of anticoagulation therapy is bleeding either from supratherapeutic effect or by accentuating the blood loss of patients with an existing source of bleeding.
- The major potential harm of withholding anticoagulation therapy is risk for thrombosis.
- Refer to the "Major Recommendations" field for additional details.
- Refer to Annotation Appendix C of the original guideline document for a list of drugs interacting with warfarin and a description of the mechanism of interaction with warfarin.

CONTRAINDICATIONS

CONTRAINDICATIONS

There are no absolute contraindications to anticoagulant therapy. The decision to treat a patient with anticoagulant drugs takes into account an individual patient's risk for thrombosis if not treated weighed against the risk of bleeding while on anticoagulation therapy. Refer to Annotation 2 in the "Major Recommendations" section for relative contraindications to warfarin therapy, Annotation 4 for contraindications in pregnancy, and to Annotation 11 for relative contraindications to heparin and derivatives.

QUALIFYING STATEMENTS

QUALIFYING STATEMENTS

- These clinical guidelines are designed to assist clinicians by providing an analytical framework for the evaluation and treatment of patients, and are not intended either to replace a clinician's judgment or to establish a protocol for all patients with a particular condition. A guideline will rarely establish the only approach to a problem.
- This clinical guideline should not be construed as medical advice or medical opinion related to any specific facts or circumstances. Patients are urged to consult a health care professional regarding their own situation and any specific medical questions they may have.

IMPLEMENTATION OF THE GUIDELINE

DESCRIPTION OF IMPLEMENTATION STRATEGY

An implementation strategy was not provided.

IMPLEMENTATION TOOLS

Patient Resources
Pocket Guide/Reference Cards

For information about availability, see the "Availability of Companion Documents" and "Patient Resources" fields below.

INSTITUTE OF MEDICINE (IOM) NATIONAL HEALTHCARE QUALITY REPORT CATEGORIES

IOM CARE NEED

Getting Better
Living with Illness
Staying Healthy

IOM DOMAIN

Effectiveness
Patient-centeredness

IDENTIFYING INFORMATION AND AVAILABILITY

BIBLIOGRAPHIC SOURCE(S)

Institute for Clinical Systems Improvement (ICSI). Anticoagulation therapy supplement. Bloomington (MN): Institute for Clinical Systems Improvement (ICSI); 2006 Apr. 49 p. [91 references]

ADAPTATION

Not applicable: The guideline was not adapted from another source.

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2001 Sep (revised 2006 Apr)

GUIDELINE DEVELOPER(S)

Institute for Clinical Systems Improvement - Private Nonprofit Organization

GUIDELINE DEVELOPER COMMENT

Organizations participating in the Institute for Clinical Systems Improvement (ICSI): Affiliated Community Medical Centers, Allina Medical Clinic, Altru Health System, Aspen Medical Group, Avera Health, CentraCare, Columbia Park Medical Group, Community-University Health Care Center, Dakota Clinic, ENT Specialty Care, Fairview Health Services, Family HealthServices Minnesota, Family Practice Medical Center, Gateway Family Health Clinic, Gillette Children's Specialty Healthcare, Grand Itasca Clinic and Hospital, HealthEast Care System, HealthPartners Central Minnesota Clinics, HealthPartners Medical Group and Clinics, Hutchinson Area Health Care, Hutchinson Medical Center, Lakeview Clinic, Mayo Clinic, Mercy Hospital and Health Care Center, MeritCare, Mille Lacs Health System, Minnesota Gastroenterology, Montevideo Clinic, North Clinic, North Memorial Care System, North Suburban Family Physicians, Northwest Family Physicians, Olmsted Medical Center, Park Nicollet Health Services, Pilot City Health Center, Quello Clinic, Ridgeview Medical Center, River Falls Medical Clinic, Saint Mary's/Duluth Clinic Health System, St. Paul Heart Clinic, Sioux Valley Hospitals and Health System, Southside Community Health Services, Stillwater Medical Group, SuperiorHealth Medical Group, University of Minnesota Physicians, Winona Clinic, Ltd., Winona Health

ICSI, 8009 34th Avenue South, Suite 1200, Bloomington, MN 55425; telephone, (952) 814-7060; fax, (952) 858-9675; e-mail: icsi.info@icsi.org; Web site: www.icsi.org.

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GUIDELINE COMMITTEE

Cardiovascular Steering Committee

COMPOSITION OF GROUP THAT AUTHORED THE GUIDELINE

Work Group Members: Bruce Burnett, MD (Work Group Leader) (Park Nicollet Health Services) (Internal Medicine); Stephen Kopecky, MD (Mayo Clinic) (Cardiology); Rajiv Pruthi, MD (Mayo Clinic) (Hematology); John Butler, MD (HealthPartners Medical Group) (Internal Medicine); Mark Morrow, MD (Aspen Medical Group) (Internal Medicine); John Davenport, MD (Park Nicollet Health

Services) (Neurology); Timothy Miley, MD (Park Nicollet Health Services) (Pathology); Jill Strykowski, RPh, MS (Park Nicollet Health Services) (Pharmacy); Brent Metfessel, MD, MPH (Institute for Clinical Systems Improvement) (Evidence Analyst); Sherri Huber, MT (ASCP) (Institute for Clinical Systems Improvement) (Facilitator)

FINANCIAL DISCLOSURES/CONFLICTS OF INTEREST

In the interest of full disclosure, the Institute for Clinical Systems Improvement (ICSI) has adopted a policy of revealing relationships work group members have with companies that sell products or services that are relevant to this guideline topic. The reader should not assume that these financial interests will have an adverse impact on the content of the guideline, but they are noted here to fully inform readers. Readers of the guideline may assume that only work group members listed below have potential conflicts of interest to disclose.

Bruce Burnett, MD, is a member of the speakers bureau for Aventis, BMS, and Astra Zeneca; a consultant for Aventis, Astra Zeneca, and Glaxo SmithKline; receives research support from Astra Zeneca.

Stephen Kopecky, MD is a consultant for Glaxo SmithKline.

Jill Strykowski, RPh received honorarium from Aventis.

No other work group members have potential conflict of interest to disclose.

ICSI's conflict of interest policy and procedures are available for review on ICSI's website at www.icsi.org.

GUIDELINE STATUS

This is the current release of the guideline.

This guideline updates a previous version: Anticoagulation therapy supplement. Bloomington (MN): Institute for Clinical Systems Improvement (ICSI); 2005 Apr. 65 p.

GUIDELINE AVAILABILITY

Electronic copies of the updated guideline: Available from the Institute for Clinical Systems Improvement (ICSI) Web site.

Print copies: Available from ICSI, 8009 34th Avenue South, Suite 1200, Bloomington, MN 55425; telephone, (952) 814-7060; fax, (952) 858-9675; Web site: www.icsi.org; e-mail: icsi.info@icsi.org.

AVAILABILITY OF COMPANION DOCUMENTS

The following are available:

- Anticoagulation therapy supplement. Executive summary. Bloomington (MN): Institute for Clinical Systems Improvement, 2006 Apr. 1 p. Electronic copies: Available from the Institute for Clinical Systems Improvement (ICSI) Web site.
- ICSI pocket guidelines. May 2005 edition. Bloomington (MN): Institute for Clinical Systems Improvement, 2005. 362 p.

Print copies: Available from ICSI, 8009 34th Avenue South, Suite 1200, Bloomington, MN 55425; telephone, (952) 814-7060; fax, (952) 858-9675; Web site: www.icsi.org; e-mail: icsi.info@icsi.org.

PATIENT RESOURCES

The following is available:

- Patient education guide to warfarin therapy. Appendix E: Anticoagulation therapy supplement. Bloomington (MN): Institute for Clinical Systems Improvement (ICSI); 2006 Apr.

Electronic copies: Available from the Institute for Clinical Systems Improvement (ICSI) Web site.

Please note: This patient information is intended to provide health professionals with information to share with their patients to help them better understand their health and their diagnosed disorders. By providing access to this patient information, it is not the intention of NGC to provide specific medical advice for particular patients. Rather we urge patients and their representatives to review this material and then to consult with a licensed health professional for evaluation of treatment options suitable for them as well as for diagnosis and answers to their personal medical questions. This patient information has been derived and prepared from a guideline for health care professionals included on NGC by the authors or publishers of that original guideline. The patient information is not reviewed by NGC to establish whether or not it accurately reflects the original guideline's content.

NGC STATUS

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